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FIRST NAMED INVENTOR ATTORNEY DOCKET NO. CONFIRMATION NO. APPLICATION NO. FILING DATE 10/714,506 11/13/2003 124263-1007 1056 Sanjay Awasthi 7590 04/03/2006 EXAMINER Monique A. Vander Molen FETTEROLF, BRANDON J Gardere Wynne Sewell LLP PAPER NUMBER ART UNIT 3000 Thanksgiving Tower 1601 Elm Street, Suite 3000 1642 Dallas, TX 75201-4767

Please find below and/or attached an Office communication concerning this application or proceeding.

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## Response to the Amendment

The Amendment filed on 01/10/2006 in response to the previous Non-Final Office Action (07/06/2005) is acknowledged and has been entered.

Claims 1-20 are pending.

Claims 12-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-11 and 19-20 are currently under consideration.

The Declaration Under CFR 1.131 filed on 01/10/2006 by the inventors, Sanjay Awasthi and Sharand S. Singhal is acknowledged and has been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

#### Rejections Maintained:

#### Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-9 remain rejected under 35 U.S.C. 102(a) as being anticipated by Awasthi *et al.* (Proc. Am. Assoc. Cancer. Res. March 2002; 43: Abs.).

Awasthi et al. teaches a method of treating 6 NSCLC cell lines undergoing uncontrolled growth comprising contacting the cells with polyclonal RLIP76 antibodies, wherein the administration of the antibodies results in apoptosis. Moreover, the reference discloses that the method further comprises administering a drug used in chemotherapy, e.g., doxorubicin, in combination with the antibody, wherein the addition of the drug to the antibody enhanced the

cytotoxicity of the drug. In addition to doxorubicin, Awasthi et al. also teach that the combination of Herceptin and anti-RLIP76 resulted in an additive effect with regards to cytotoxicity. Although Awasthi et al does not specifically teach that the antibody to RLIP76 inhibits the transport activity of RLIP76 resulting in the prevention of a drug from leaving the cell, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Sharma et al. (Arch. Biochem. Biophys. 2001; 391: 171-179) ATP dependent inhibition of the ATP-dependent transport of DOX was inhibited in erythrocyte inside-out vesicles coated with antibodies against RLIP76 (Abstract). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

In response to this rejection, Applicants have submitted a signed Declaration under 37 CFR 1.131 by the Applicants establishing that the Awasthi 2002 reference is describing Applicant's own work. Accordingly, Applicants submit that the subject matter considered prior art under 35 USC 102 (a) is now disqualified as prior art against this Application for invention.

The Declaration Under CFR 1.131 filed on 01/10/2006 has been considered but is ineffective to overcome the Awasthi *et al.* reference. In the instant case, the Examiner acknowledges that Applicants have provided an appropriate oath or declaration to establish invention of the subject matter of the rejected claims prior to the effective date of the reference or activity on which the rejection is based. However, the Examiner recognizes that Applicants have provided no facts, i.e., original exhibits of drawings or records, or photocopies thereof, which must accompany and form part of the affidavit or declaration, see MPEP, CFR 1.131. As such, Claims 1 and 3-9 remain rejected under 35 U.S.C. 102(a) as being anticipated by Awasthi *et al.* (Proc. Am. Assoc. Cancer. Res. March 2002; 43: Abs.)

Claims 1 and 3-9 remain rejected under 35 U.S.C. 102(b) as being anticipated by Awasthi et al. (Proc. Am. Assoc. Cancer. Res. March 2001; 42: Abst.).

Awasthi et al. teach a method of treating both SCLC and NSCLC cell lines undergoing uncontrolled growth comprising contacting the cells with anti-RLIP76 antibodies which recognize a cell surface epitope in lung cancer cells. The reference further teaches that the administration of anti-RLIP76 to the cells resulted in DNA laddering demonstrating apoptotic activity. Moreover, Awasthi et al. discloses that the method further comprises administering a drug used in chemotherapy, e.g., doxorubicin, in combination with the antibody, wherein the addition of the drug to the antibody enhanced the cytotoxicity of the drug. Although Awasthi et al. does not specifically teach that the antibody to RLIP76 inhibits the transport activity of RLIP76 resulting in the prevention of a drug from leaving the cell, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Sharma et al. (Arch. Biochem. Biophys. 2001; 391: 171-179) ATP dependent inhibition of the ATP-dependent transport of DOX was inhibited in erythrocyte inside-out vesicles coated with antibodies against RLIP76 (Abstract). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

In response to the rejection, Applicants submit that claim 1 has been amended to recite a method of "treating one or more cells undergoing uncontrolled growth comprising the steps of contacting one or more cells with an antibody to <u>ralA biding protein1</u>, wherein the direct contact is <u>cytotoxic to one or more cells in the absence or an additional agent.</u>" (Emphasis indicating amended text). As such, Applicants contend that Awasthi 2001 does not disclose or suggest contacting one or more cells with an antibody to ral1A binding protein1, wherein the direct contact is cytotoxic to the one or more cells in the absence of an additional agent. Instead, Applicants assert that Awasthi 2001

discloses that "antibodies markedly augment the cytoxicity of doxorubicin," but this is not equivalent to the antibodies themselves being cytotoxic. For example, Applicants submit that many chemotherapeutic agents exhibit enhanced cytotoxicity when combined with a non-chemotherapeutic compound or agent, but the non-chemotherapeutic compound is no, itself chemotherapeutic. Thus, Applicants argue that Awasthi 2001 does not teach each and every element of amended claim 1.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicant's contention that Awasthi 2001 does not anticipate amended claim 1 because Awasthi 2001 only teaches that antibodies markedly augment the cytotoxicity of doxorubin and not that the direct contact of the antibody to one or more cells is cytotoxic in the absence of an additional agent, the Examiner acknowledges and agrees with Applicants assertion that Awasthi 2001 teaches antibodies which markedly augment the cytotoxicity of doxorubin. However, the Examiner recognizes that in addition to this teaching, Awasthi 2001 discloses the use of anti-RLIP76 antibodies alone. For example, as state *supra*, Awasthi 2001 teaches that the administration of anti-RLIP76 alone to SCLC and NSCLC cells resulted in DNA laddering which demonstrates apoptotic activity. Moreover, Awasthi 2001 teaches that the anti-RLIP76 antibodies are useful as a therapeutic modality for lung cancer, both alone and in combination with chemotherapy. As such, claims 1 and 3-9 remain rejected under 35 U.S.C. 102(b) as being anticipated by Awasthi *et al.* (Proc. Am. Assoc. Cancer. Res. March 2001; 42: Abst.).

#### Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Awasthi et al. (Proc. Am. Assoc. Cancer. Res. March 2001; 42: Abst.) in combination with American Type Culture Collection (Tumor Cell Lines, 2001).

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Awasthi et al. teaches a method of treating both SCLC and NSCLC cell lines undergoing uncontrolled growth comprising contacting the cells with anti-RLIP76 antibodies which recognize a cell surface epitope in lung cancer cells.

Awasthi *et al.* does not teach that the cells are selected from the group of cancerous cells consisting of NCI-H82, NCI-H182, NCI-1417, NCI-1618, NCI-H1395, NCI-H2347, HCC44 (adenocarcinoma), and NCI-H2126.

American Type Culture Collection discloses a plethora of commercially available tumor cell lines including but not limited cell lines obtained from SCLC and NSCLC such as NCI-H82, NCI-1417, NCI-1618, NCI-H1395, NCI-H2341 and NCI-H2126.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a SCLC or NSCLC tumor cell line in the method of Awasthi *et al.*. One would have been motivated to do so because the American Type Culture Collection discloses commercially available lung tumor cell lines, SCLC and NSCLC, while Awasthi *et al.* teaches a method of treating SCLC and NSCLC cell lines undergoing uncontrolled cell growth with RLIP76 antibodies which specifically recognize an epitope in lung cancer cells. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by combining a SCLC or NSCLC tumor cell line available through ATCC with the method as taught by Awasthi et al., one would achieve a method of treating uncontrolled cell growth in at least NCI-H82, NCI-1417, NCI-1618, NCI-H1395, NCI-H2341 and NCI-H2126 cells. Vacuum

In response to this rejection, Applicants contend claims 1-9 are not anticipated by Awasthi 2001 for the reasons set forth above and therefore, combining Awasthi 2001 with ATCC does not overcome the fundamental failure of Awasthi 2001 to anticipate each and every element of independent and amended claim 1 or amended claim 1 on its whole. Applicants further submit that ATTC does not suggest or teach contacting one or more cells with an antibody to ralA biding protein1, wherein the direct contact is cytotoxic to one or more cells in the absence of an additional agent. Thus, combining ATTC with Awasthi 2001 does not overcome the deficiencies of Awasthi 2001 as described above nor does the combination teach Applicants claimed invention on its whole. Moreover, Applicants assert that there is no teaching or suggestion in Awasthi 2001 or in ATCC to modify or combine the references in such a way that would resemble Applicants' invention as

claimed in amended claim 1; nor is there any indication of a reasonable expectation of success if such references were to be combined.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments pertaining to Awasthi 2001 not anticipating amended claim 1 have been addressed above. Regarding Applicants assertion that ATTC does not suggest or teach contacting one or more cells with an antibody to ralA binding protein1, the Examiner acknowledges that ATCC does not explicitly teach contacting one or more cells with an antibody to ralA binding protein 1. However, the Examiner recognizes that it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the suggestion to combine was based on the commercial availability of the tumor cell lines obtained from SCLC and NSCLC and the suggestion by Awasthi 2001 that SCLC and NSCLC cell lines undergoing uncontrolled cell growth are treated with RLIP76 antibodies which specifically recognize an epitope in lung cancer cells. Therefore, Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination.

Claims 1-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Awasthi et al. (Proc. Am. Assoc. Cancer. Res. March 2001; 42: Abst.) in view of Sause WT (Chest, 1999; 116: 504S-508S).

Awasthi et al. teaches a method of treating both SCLC and NSCLC cell lines undergoing uncontrolled growth comprising contacting the cells with RLIP76 antibodies which recognize a cell surface epitope in lung cancer cells, wherein ant-RLIP76 promotes apoptosis in the cell.

Awasthi *et al.* does not teach that the antibody is added in combination with radiation therapy.

Sause teaches the role of radiotherapy in non-small cell lung cancer. Specifically, the reference teaches that radiation therapy (RT) is an effective method of local disease control for non-small lung cancer (NSCLC) and can be used for definitive management in selected patients (page 504S, 1<sup>st</sup> column, 1<sup>st</sup> paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat one or more cells undergoing uncontrolled growth. One of skill in the art would have been motivated to so because each of the therapeutics had been individually taught in the prior art to be successful at treating cells undergoing uncontrolled growth such as cancer. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, one of ordinary skill in the art would have reasonably expected that by adding RLIP76 antibodies in combination with radiation therapy, one would achieve an enhanced method of treating cell undergoing uncontrolled growth.

Moreover, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to this rejection, Applicants contend that claims 1-11 are not anticipated by Awasthi 2001 for the reasons set forth above. Thus, Applicants assert that combining Awasthi 2001 with Sause, which is non-analogous art that teaches the role of radiotherapy in non-small cell lung cancer, does not overcome the failure of Awasthi 2001 to anticipate each and every element of the independent and amended claim 1 or amended claim 1 on its while. For example, Applicants argue that Sause does not suggest or teach contacting one or more cells with an antibody to ralA binding protein 1, wherein the direct contact is cytotoxic to one or more cells in the absence of an additional agent. In fact, Applicants point out that Sause teaches combining treatments such as radiation and chemotherapy and does not teach or suggest using an antibody to ralA binding protein1 or using it

in the absence of an additional agent. Moreover, Applicants assert that there is no teaching or suggestion in Awasthi 2001 and Sause to modify or combine the references in such a way that would resemble Applicant's invention as claimed in amended claim 1; nor is there any indication of a reasonable expectation of success if such references were to be combined. Accordingly, Applicants submit that amended claims 1 and its dependents are patentably distinct from the cited art.

These arguments have been carefully considered, but are not found persuasive.

First, Applicants arguments pertaining to Awasthi 2001 not anticipating amended claim 1 have been addressed above. Regarding Applicants assertion that Sause does not suggest or teach contacting one or more cells with an antibody to ralA binding protein1, the Examiner acknowledges that Sause does not explicitly teach contacting one or more cells with an antibody to ralA binding protein1. However, the Examiner recognizes that it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, one of skill in the art would have been motivated to combine the two references because each of the therapeutics had been individually taught in the prior art to be successful at treating cells undergoing uncontrolled growth such as cancer. As such, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Therefore, claims 1-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Awasthi et al. (Proc. Am. Assoc. Cancer. Res. March 2001; 42: Abs.) in view of Sause WT (Chest, 1999; 116: 504S-508S).

## New Rejections necessitated by amendment:

## Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claim 19 has been amended to recite a method of locating a cell undergoing uncontrolled growth comprising the steps of: contacting one or more cells with an antibody to ralA binding protein1, wherein the antibody is connected to a tracer molecule and the tracer molecule is capable of identifying the location of the one or more cells in the absence of an additional agent. (Emphasis indicating the amended limitation) While the specification teaches cytotoxicity of anti-RLIP76 in the absence of an additional agent (page 27, line 14), the specification as originally filed does not appear to have support for the limitation "in the absence or an additional agent" in the context of a method of locating a cell undergoing uncontrolled growth. Applicant is invited to point to clear support or specific examples of the claimed limitation in the specification as-filed or remove such amendatory language in response to this office action.

Note: Applicant's arguments and amendment to claim 19 have overcome the rejection of claims 19-20 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 2002/0119156, 2001) in combination with Awasthi et al. (Proc. Am. Assoc. Cancer. Res. March 2001; 42: Abst.) because the combination does not teach or suggest identifying the location of one or more cells in the absence of an additional agent. However, if applicants were to amend claim 19 to overcome the new matter rejection, supra, the prior art would be reapplied.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

### Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD

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